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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,442	07/10/2001	Lawrence M. Kauvar	25352-0003P8-1	8907

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,442	KAUVAR ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-1-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 10-1-04 is acknowledged.

Claims included in the prosecution are 61-81.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 61-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauvar et al (5,955,432) or WO 96/40205 cited in the previous action, further in view of the references of Young (5,023,087), Lambiez (5,605,703) and Uster (4,944,948) by themselves or in combination.

The teachings of Kauvar et al, and WO have been discussed above. In essence, Kauvar et al and WO both disclose a method of stimulating hematopoiesis using the same claimed compounds. Although Kauvar et al and WO do not show the administration of the compounds in liposomal form, through examples, both suggest the use of liposomes for the delivery of the compounds (see col. 7, lines 17-19 of 432; page 12, lines 27-29 of WO).

What are lacking in these references however, are the teachings of the use of specific liposomes, that is, negatively charged liposomes.

Young while disclosing liposomal formulations for the delivery of a variety of drugs teaches that the liposomes allow the selected compound to be released in the blood stream at a slow, controlled rate over a several hours to several days period, thus avoiding the large fluctuations in drug blood levels that are characteristic of free drug administration. Young further teaches that one advantage of his formulation is the increased stability of a pharmaceutical compound, which is achieved with liposome encapsulation. Young's liposomes are made from egg PC and PG (abstract; col. 7, line 58 through col. 8, line 18; col. 9, line 65 through col. 10, line 49; col. 16, line 34 et seq., col. 18, line 45 et seq., Examples).

Lambiez while disclosing doxorubicin-containing liposomes teaches that the inclusion of a negatively charged phospholipid favors the stability of the liposome solution. Lambiez also teaches high encapsulation efficiencies of these liposomes. The ratios of the neutral phospholipid to the negative phospholipid taught are 10:2 to 10: 10 (abstract, col. 4, lines 24-39, Table II on col.9 and claims).

Uster while disclosing liposomal formulations for EGF teaches EPC: EPG in equal ratios of 1:1. According to Uster these liposomes enhance the half-life of EGF several fold over free EGF.

The use of liposomes, in particular negatively charged liposomes containing PC and PG for the delivery of the compounds of Kauvar et al or WO would have been obvious to one of ordinary skill in the art because of the advantages of liposomes as delivery devices as taught by Young and the advantages of negatively charged liposomes containing PG as taught by Lambiez and Uster.

3. Claims 61-81are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan et al (Cancer Chemother. Pharmacol. 37, 363-370, 1996) cited in the previous action, further in view of the references of Young (5,023,087), Lambiez (5,605,703) and Uster (4,944,948) by themselves or in combination.

Morgan et al disclose a method of administration of the claimed compounds to potentiate the effect of chemotherapeutic compounds (abstract, Materials and Methods, Tables and Figures).

What are lacking in Morgan et al are the teachings of the use of liposomes for the delivery of the compounds.

Young while disclosing liposomal formulations for the delivery of a variety of drugs teaches that the liposomes allow the selected compound to be released in the blood stream at a slow, controlled rate over a several hours to several days period, thus avoiding the large fluctuations in drug blood levels that are characteristic of free drug administration. Young further teaches that one advantage of his formulation is the increased stability of a pharmaceutical compound, which is achieved with liposome encapsulation. Young's liposomes are made from egg PC and PG (abstract; col. 7, line 58 through col. 8, line 18; col. 9, line 65 through col. 10, line 49; col. 16, line 34 et seq., col. 18, line 45 et seq., Examples).

Lambiez while disclosing doxorubicin-containing liposomes teaches that the inclusion of a negatively charged phospholipid favors the stability of the liposome solution. Lambiez also teaches high encapsulation efficiencies of these liposomes. The

ratios of the neutral phospholipid to the negative phospholipid taught are 10:2 to 10: 10 (abstract, col. 4, lines 24-39, Table II on col.9 and claims).

Uster while disclosing liposomal formulations for EGF teaches EPC: EPG in equal ratios of 1:1. According to Uster these liposomes enhance the half-life of EGF several fold over free EGF.

The use of liposomes, in particular negatively charged liposomes containing PC and PG for the delivery of the compounds of Morgan et al would have been obvious to one of ordinary skill in the art because of the advantages of liposomes as delivery devices as taught by Young and the advantages of negatively charged liposomes containing PG as taught by Lambiez and Uster.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 61-81 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims1-38 of U.S. Patent No.

5,955,432 in view of the references of Young (5,023,087), Lambiez (5,605,703) and Uster (4,944,948) by themselves or in combination.

The claims in both said patent and instant application are drawn to the same compounds and method of stimulating hematopoiesis or method of potentiating a chemotherapeutic compound effect and the claims in the said patent recite esters of the compounds and instant diesters therefore, come under the generic term in said patent. As pointed out above, the claims in said patent do not recite lipid carrier or specifically negatively charged liposomes as carriers. The patent in the specification however, recites liposomes as carriers.

Young while disclosing liposomal formulations for the delivery of a variety of drugs teaches that the liposomes allow the selected compound to be released in the blood stream at a slow, controlled rate over a several hours to several days period, thus avoiding the large fluctuations in drug blood levels that are characteristic of free drug administration. Young further teaches that one advantage of his formulation is the increased stability of a pharmaceutical compound, which is achieved with liposome encapsulation. Young's liposomes are made from egg PC and PG (abstract; col. 7, line 58 through col. 8, line 18; col. 9, line 65 through col. 10, line 49; col. 16, line 34 et seq., col. 18, line 45 et seq., Examples).

Lambiez while disclosing doxorubicin-containing liposomes teaches that the inclusion of a negatively charged phospholipid favors the stability of the liposome solution. Lambiez also teaches high encapsulation efficiencies of these liposomes (abstract, col. 4, line 24 et seq., Table II on col.9 and claims).

Uster while disclosing liposomal formulations for EGF teaches EPC: EPG in equal ratios of 1:1. According to Uster these liposomes enhance the half-life of EGF several fold over free EGF.

The use of liposomes, in particular negatively charged liposomes containing PC and PG for the delivery of the compounds of 5,955,432 would have been obvious to one of ordinary skill in the art because of the advantages of liposomes as delivery devices as taught by Young and the advantages of negatively charged liposomes containing PG as taught by Lambiez and Uster.

Applicant's arguments have been fully considered, but are deemed to be moot in view of these new rejections. However, the examiner would like to address applicant's arguments with regard to the references of Young and Lambiez, which were used in the previous action. Applicant argues that Young's ratios are outside the claimed ratios. This argument is not found to be persuasive since Young is combined for its teachings of the advantages in using liposomes in general and the references of Lambiez and Uster show the claimed ratios. Applicant argues that Lambiez gives only broad guidance and that the liposomes of Lambiez also contain cholesterol. These arguments are not found to be persuasive since Lambiez is suggestive of the use of equal amounts of PC and PG. With regard to cholesterol in Lambiez, the examiner points out that instant claims do not exclude cholesterol.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GSK Kishore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK